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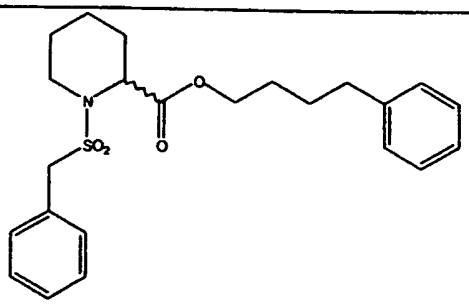
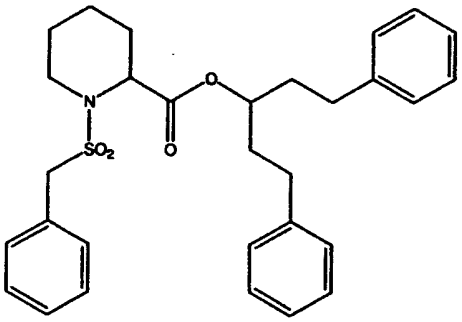
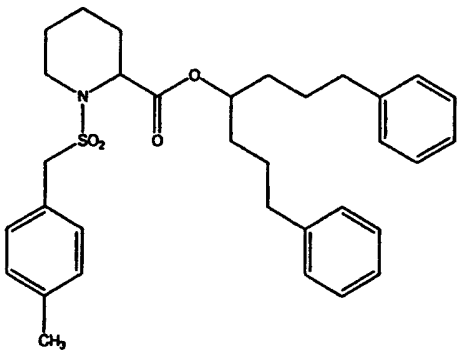
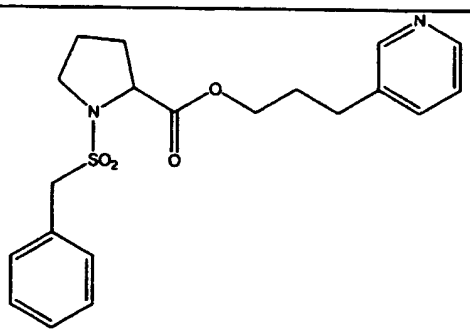
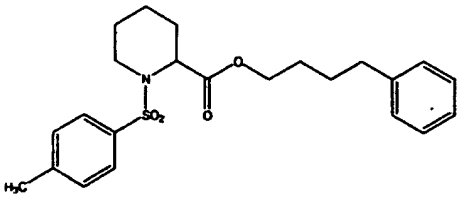
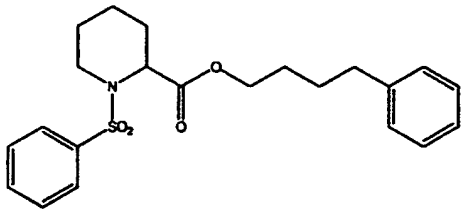
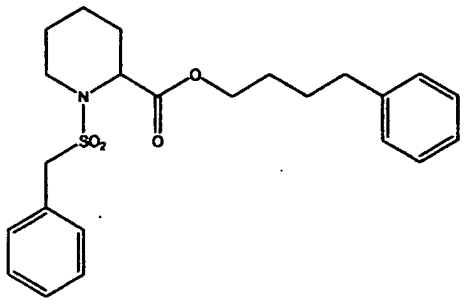
(54) Title: METHOD FOR PREVENTING AND TREATING HEARING LOSS USING SENSORINEUROTROPHIC COMPOUNDS

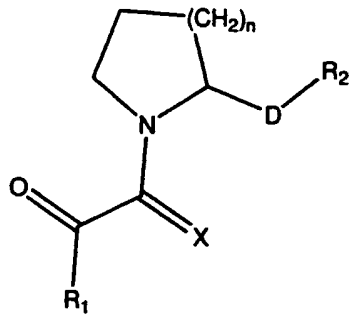
Table XL

Cpd.	Structure and name
278	 4-phenyl-1-butyl-1-(benzylsulfonyl)-(2R,S)-2-pipecolinate
279	 1,5-diphenyl-3-pentyl-N-(a-toluenesulfonyl)-pipecolate
280	 1,7-diphenyl-4-heptyl-N-(para-toluene-sulfonyl)pipecolate

Cpd.	Structure and name
281	 3-(3-pyridyl)-1-propyl-(2S)-N-(a-toluenesulfonyl)-pyrrolidine-2-carboxylate
282	 4-phenyl-1-butyl-N-(para-toluenesulfonyl)pipecolate
283	 4-phenyl-1-butyl-N-(benzenesulfonyl)-pipecolate
284	 4-phenyl-1-butyl-N-(a-toluenesulfonyl)pipecolate

VII. Carboxylic Acid Isosteres as Sensorineuro-trophic Compounds

Another especially preferred embodiment of the invention is a compound of formula (LXIV):



(LXIV)

in which:

n is 1-3;

X is either O or S;

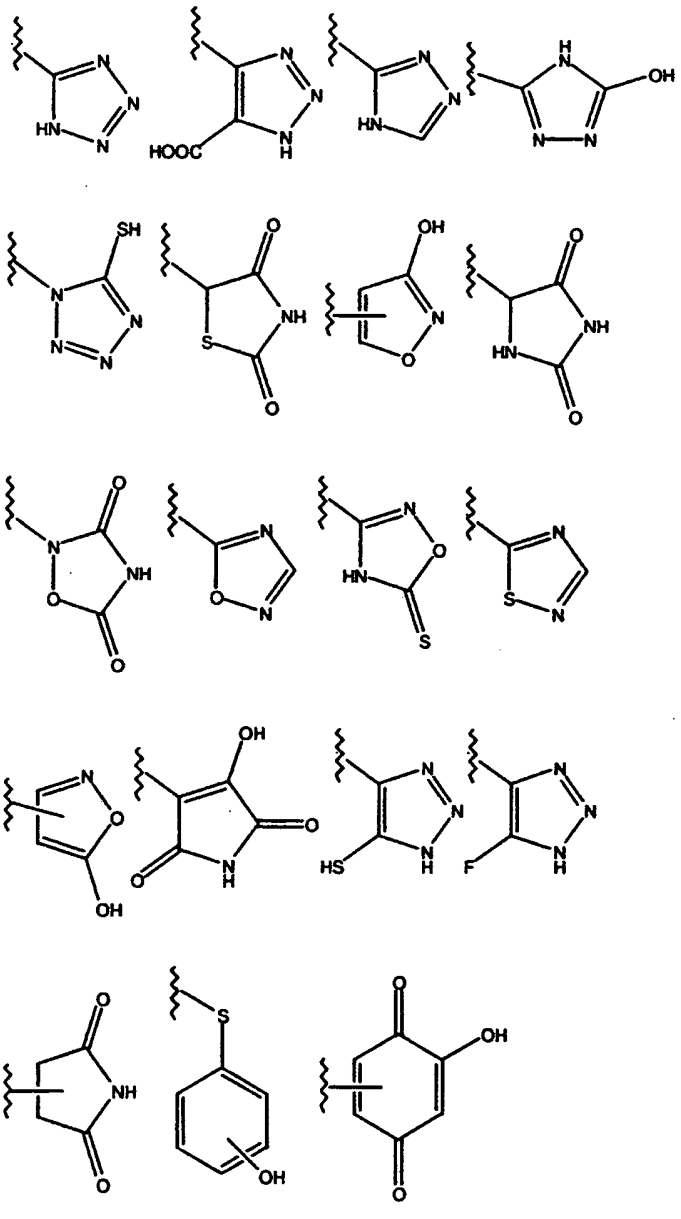
R_1 is selected from the group consisting of C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C_1-C_{10} straight or branched chain alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl; and

R_2 is a carboxylic acid or a carboxylic acid isostere; or a pharmaceutically acceptable salt, ester, or solvate thereof;

Preferred embodiments of this invention are where R_2 is a carbocycle or heterocycle containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions with R^3.

Especially preferred embodiments of this invention are where R_2 is selected from the group below:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3.

Another preferred embodiment of this invention is where R_2 is selected from the group consisting of -COOH, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, -CN, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$, $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$, $-COHNSO_2R^3$, and $-CONR^3CN$ wherein R^3 is hydrogen, hydroxy, halo, halo-C_1-C_6-alkyl, thiocarbonyl, C_1-C_6-alkoxy, C_2-C_6-alkenoxy, C_1-C_6-alkylaryloxy, aryloxy, aryl- C_1-C_6-alkyloxy, cyano, nitro, imino, C_1-C_6-alkylamino, amino-C_1-C_6-alkyl, sulfhydryl, thio- C_1-C_6-alkyl, C_1-C_6-alkylthio, sulfonyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, and CO_2R^4 where R^4 is hydrogen or C_1-C_9 straight or branched chain alkyl or alkenyl.

Preferred embodiments of this invention are: (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-hydroxymethyl pyrrolidine; (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinetetrazole; (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarbonitrile; and (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-aminocarbonyl piperidine.

A compound of the present invention, especially formula LXIV, wherein n is 1, X is O, D is a bond, R_1 is 1,1,dimethylpropyl, and R_2 is -CN, is named (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidine-carbonitrile.

Specific embodiments of the inventive compounds are presented in Tables XLI, XLII, and XLIII. The present invention contemplates employing the compounds of Tables XLI, XLII and XLIII, below.

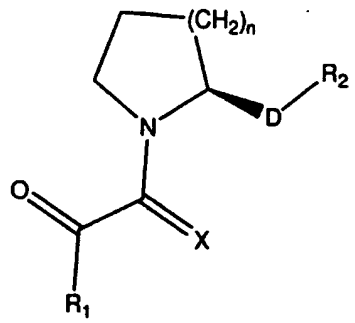
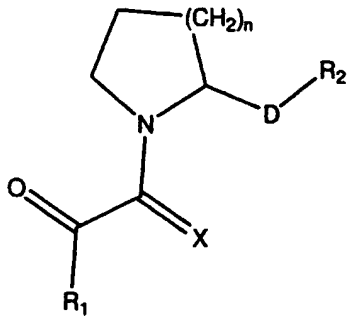


Table XLI

when D is a bond and R2 is COOH,

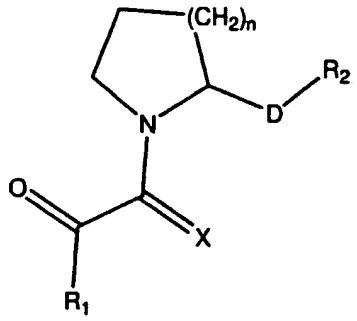
No.	X	n	R_1
285	O	1	3,4,5-trimethylphenyl
286	O	2	3,4,5-trimethylphenyl
287	O	1	tert-butyl
287	O	3	tert-butyl
288	O	1	cyclopentyl
289	O	2	cyclopentyl
290	O	3	cyclopentyl
291	O	1	cyclohexyl
292	O	2	cyclohexyl
293	O	3	cyclohexyl
294	O	1	cycloheptyl
295	O	2	cycloheptyl
296	O	3	cycloheptyl
297	O	1	2-thienyl
298	O	2	2-thienyl
299	O	3	2-thienyl
300	O	1	2-furyl
301	O	2	2-furyl
302	O	3	2-furyl
303	O	3	phenyl
304	O	1	1,1-dimethylpentyl
305	O	2	1,1-dimethylhexyl
306	O	3	ethyl
307			

Table XLII



No.	X	n	R_1	D	R_2
308	S	1	1,1-dimethyl propyl	CH_2	COOH
309	S	1	1,1-dimethyl propyl	bond	COOH
310	O	1	1,1-dimethyl propyl	CH_2	OH
311	O	1	1,1-dimethyl propyl	bond	SO_3H
312	O	1	1,1-dimethyl propyl	CH_2	CN
313	O	1	1,1-dimethyl propyl	bond	CN
314	O	1	1,1-dimethyl propyl	bond	tetrazolyl
315	S	1	phenyl	$(CH_2)_2$	COOH
316	S	1	phenyl	$(CH_2)_3$	COOH
317	S	2	phenyl	CH_2	COOH
318	O	1	1,1-dimethyl propyl	bond	$CONH_2$
319	O	2	1,1-dimethyl propyl	bond	$CONH_2$
320	S	2	2-furyl	bond	PO_3H_2
321	O	2	propyl	$(CH_2)_2$	COOH
322	O	1	propyl	$(CH_2)_3$	COOH
323	O	1	tert-butyl	$(CH_2)_4$	COOH
324	O	1	methyl	$(CH_2)_5$	COOH
325	O	2	phenyl	$(CH_2)_6$	COOH
326	O	2	3,4,5- trimethoxy-phenyl	CH_2	COOH
327	O	2	3,4,5- trimethoxy-phenyl	CH_2	tetrazolyl

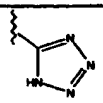
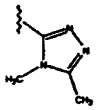
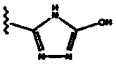
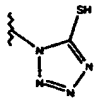
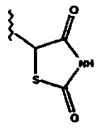
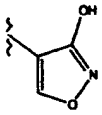
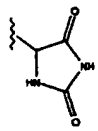
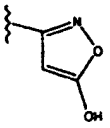
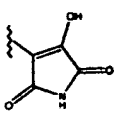
TABLE XLIII

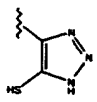
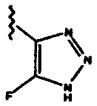
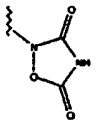
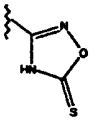
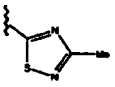
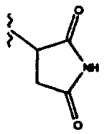
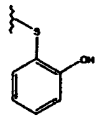
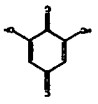


No.	n	X	D	R_2	R_1
328	1	S	bond	COOH	Phenyl
329	1	O	bond	COOH	a-MethylBenzyl
330	2	O	bond	COOH	4-MethylBenzyl
331	1	O	bond	Tetrazole	Benzyl
332	1	O	bond	SO_3H	a-MethylBenzyl
333	1	O	CH_2	COOH	4-MethylBenzyl
334	1	O	bond	SO_2HNMe	Benzyl
335	1	O	bond	CN	a-MethylBenzyl
336	1	O	bond	PO_3H_2	4-MethylBenzyl
337	2	O	bond	COOH	Benzyl
338	2	O	bond	COOH	a-MethylBenzyl
339	2	O	bond	COOH	4-MethylBenzyl
340	2	S	bond	COOH	3,4,5-trimethoxyphenyl
341	2	O	bond	COOH	Cyclohexyl
342	2	O	bond	PO_2HEt	i-propyl
343	2	O	bond	$PO_3HPropyl$	ethyl
344	2	O	bond	$PO_3(Et)_2$	Methyl
345	2	O	bond	OMe	tert-butyl
346	1	O	bond	OEt	n-pentyl
347	2	O	bond	OPropyl	n-hexyl
348	1	O	bond	OButyl	Cyclohexyl
349	1	O	bond	OPentyl	cyclopentyl
350	1	O	bond	OHexyl	n-heptyl
351	1	O	bond	SMe	n-octyl
352	1	O	bond	SEt	n-nonyl
353	2	O	bond	SPropyl	2-indolyl
354	2	O	bond	SButyl	2-furyl
355	2	O	bond	NHCOMe	2-thiazolyl

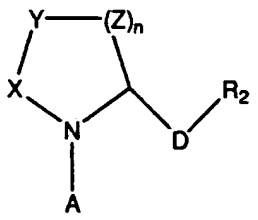
No.	n	X	D	R_2	R_1
356	2	O	bond	NHCOEt	2-thienyl
357	1	O	CH_2	$N(Me)_2$	2-pyridyl
358	1	O	$(CH_2)_2$	N(Me)Et	1,1-dimethylpropyl
359	1	O	$(CH_2)_3$	$CON(Me)_2$	1,1-dimethylpropyl
360	1	O	$(CH_2)_4$	CONHMe	1,1-dimethylpropyl
361	1	O	$(CH_2)_5$	CONHEt	1,1-dimethylpropyl
362	1	O	$(CH_2)_6$	CONHPropyl	1,1-dimethylpropyl
363	1	O	bond	CONH(O)Me	Benzyl
364	1	O	bond	CONH(O)Et	a-Methylphenyl
365	1	O	bond	CONH(O)Propyl	4-Methylphenyl
366	1	O	$(CH_2)_2$	COOH	Benzyl
367	1	O	bond	COOH	a-Methylphenyl
368	1	O	bond	COOH	4-Methylphenyl
369	1	O	CH_2	COOH	1,1-dimethylpropyl
370	1	O	$(CH_2)_2$	COOH	1,1-dimethylbutyl
371	1	O	$(CH_2)_3$	COOH	1,1-dimethylpentyl
372	1	O	$(CH_2)_4$	COOH	1,1-dimethylhexyl
373	1	O	$(CH_2)_5$	COOH	1,1-dimethylethyl
374	1	O	$(CH_2)_6$	COOH	iso-propyl
375	1	O	$(CH_2)_7$	COOH	tert-butyl
376	1	O	$(CH_2)_8$	COOH	1,1-dimethylpropyl
377	1	O	$(CH_2)_9$	COOH	benzyl
378	1	O	$(CH_2)_{10}$	COOH	1,1-dimethylpropyl
379	1	O	C_2H_2	COOH	cyclohexylmethyl
380	1	O	2-OH,Et	COOH	1,1-dimethylpropyl
381	1	O	2-butylene	COOH	1,1-dimethylpropyl
382	1	S	*i*-Pro	COOH	1,1-dimethylpropyl
383	2	S	*t*-Bu	COOH	phenyl
384	2	O	2-NO_2-hexyl	COOH	1,1-dimethylpropyl
385	1	O	$(CH_2)_2$	CN	1,1-dimethylpropyl
386	1	O	$(CH_2)_3$	CN	1,1-dimethylpropyl
387	3	O	bond	$CONHNHSO_2Me$	Benzyl
388	3	O	bond	$CONHNHSO_2Et$	a-Methylphenyl
389	3	O	bond	$CONHSO_2Me$	4-Methylphenyl
390	1	O	bond	$CONHNHSO_2Et$	Phenyl
391	2	O	bond	CON(Me)CN	a-Methylphenyl
392	1	O	bond	CON(Et)CN	4-Methylphenyl
393	1	O	$(CH_2)_2$	COOH	methyl

No.	n	X	D	R_2	R_1
394	1	O	$(CH_2)_3$	COOH	ethyl
395	1	O	$(CH_2)_4$	COOH	n-propyl
396	1	O	$(CH_2)_5$	COOH	t-butyl
397	1	O	$(CH_2)_6$	COOH	Pentyl
398	1	O	$(CH_2)_7$	COOH	Hexyl
399	1	O	$(CH_2)_8$	COOH	Heptyl
400	1	O	$(CH_2)_9$	COOH	Octyl
401	1	O	C_2H_2	COOH	Cyclohexyl

No.	n	X	D	R_2	R_1
402	2	O	bond		1,1-dimethylpropyl
403	1	O	bond		1,1-dimethylpropyl
404	1	O	bond		1,1-dimethylpropyl
405	1	O	bond		1,1-dimethylpropyl
406	1	O	bond		1,1-dimethylpropyl
407	1	O	bond		1,1-dimethylpropyl
408	1	O	bond		1,1-dimethylpropyl
409	1	O	bond		1,1-dimethylpropyl
410	1	O	bond		1,1-dimethylpropyl
411	1	O	bond		1,1-dimethylpropyl

No.	n	X	D	R_2	R_1
412	1	O	bond		1,1-dimethylpropyl
413	1	O	bond		1,1-dimethylpropyl
414	1	O	bond		1,1-dimethylpropyl
415	1	O	bond		1,1-dimethylpropyl
416	1	O	bond		1,1-dimethylpropyl
417	1	O	bond		1,1-dimethylpropyl
418	1	O	bond		1,1-dimethylpropyl
419	1	O	bond		1,1-dimethylpropyl
420	1	O	bond		1,1-dimethylpropyl
421	1	O	bond	COOH	1,1-dimethylpropyl
422	2	O	bond	COOH	1,1-dimethylpropyl

Another preferred embodiment of this aspect of the invention is the use for treating or preventing sensorineural hearing loss of a compound of the formula (LXV):



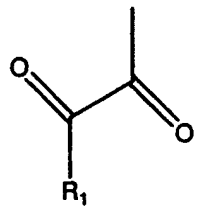
(LXV)

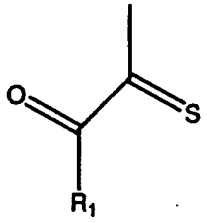
in which

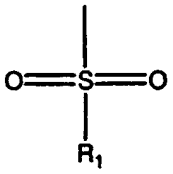
X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

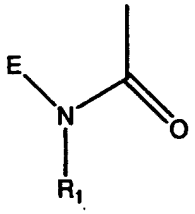
n is 1-3;

A is selected from the group consisting of L_1, L_2, L_3, or L_4, in which

L_1 is  ,

L_2 is 

L_3 is  ,

and L_4 is 

and R_1 and E, independently, are selected from the group consisting of hydrogen, C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

R_2 is carboxylic acid or a carboxylic acid isostere;

wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents

selected from R^3, where

R^3 is hydrogen, hydroxy, halo, halo(C_1-C_6)-alkyl, thiocarbonyl, (C_1-C_6)-alkoxy, (C_2-C_6)-alkenoxy, (C_1-C_6)-alkylaryloxy, aryloxy, aryl-(C_1-C_6)-alkyloxy, cyano, nitro, imino, (C_1-C_6)-alkylamino, amino-(C_1-C_6)-alkyl, sulfhydryl, thio-(C_1-C_6)-alkyl, (C_1-C_6)-alkylthio, sulfonyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO_2R^4 where R^4 is hydrogen or C_1-C_9 straight or branched chain alkyl or alkenyl;

or a pharmaceutically acceptable salt, ester, or solvate thereof;

Preferred embodiments of this embodiment of the invention are those in which R_2 is a carbocycle or heterocycle containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions with R^3.

Especially preferred embodiments of this aspect of the invention are the use of those compounds in which R_2 is selected from the group below: